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ATLAS A pragmatic randomised double-blind trial of Antipsychotic Treatment of very LAte-onset Schizophrenia-like psychosis

Very late-onset schizophrenia-like psychosis is a common condition, which affects an estimated 34,000 of the UK population aged over 60 and with 2,800 new service contacts each year. After dementia and depression, these patients represent the largest diagnostic group presenting to Old Age Psychiatry services. Impairments in quality of life associated with psychosis are severe and comparable to those seen in younger schizophrenia patients and elderly people with dementia. Patients often suffer the effects of their delusional beliefs for 10 or 20 years and this has a negative impact upon their families, neighbours and local social and housing services.

Antipsychotic drugs are widely used to treat late-onset schizophrenia-like psychosis patients but the balance of benefits and risks of this approach have not been properly evaluated. A Cochrane review concludes that there is no reliable clinical trial evidence upon which to base treatment guidelines. Antipsychotic drugs may increase the risk of stroke and death. This risk needs to be balanced against potential benefits of such treatment, which cannot currently be quantified without clinical trial evaluation. A large randomised trial is urgently needed to assess reliably the value of antipsychotic drugs in late-onset schizophrenia-like psychosis. The National Institute for Health Research's Health Technology Assessment programme has, therefore, funded such a trial, **ATLAS** ("Antipsychotic Treatment of very LAte-onset Schizophrenia-like psychosis").

ATLAS is a double-blind placebo-controlled trial, in patients with very late-onset schizophrenia-like psychosis, to evaluate whether giving 12 weeks treatment with a low dose of the antipsychotic drug, amisulpride, produces sufficient benefit to outweigh the potential risks. **ATLAS** also evaluates whether prolonging treatment for a further 24 weeks among patients who have already been treated with amisulpride for 12 weeks, confers additional benefit. The primary outcome measures are change in the Brief Psychiatric Rating Scale (BPRS) score and the proportions who discontinue treatment because of a perceived lack of efficacy. **ATLAS** will also assess side-effects, safety, the effects of treatment on quality of life and the cost-effectiveness of amisulpride treatment. As well as evaluating therapeutic approaches, **ATLAS** provides a unique opportunity to obtain a better understanding of the risk factors and natural history of late-onset schizophrenia-like psychosis and to identify patient characteristics predictive of response to antipsychotic therapy.

ATLAS aims to randomise 300 patients, in a 2:1 ratio, between 12 weeks of amisulpride and matching placebo. Patients allocated placebo will then switch to amisulpride whereas those receiving amisulpride will be randomised to continuing with either amisulpride or placebo. Thus all patients receive some active treatment. To make widespread participation feasible, trial procedures and documentation are kept to a minimum. Although recruiting 300 patients will be challenging, this is a small number compared to the many tens of thousands of future patients whose treatment will be guided by the results of **ATLAS**. The success of the study depends on the wholehearted support of the old-age psychiatry community. Publication of the main results will therefore be in the names of all collaborators and not those of the central organisers.

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1. BACKGROUND & RATIONALE

There are two main groups of older people with schizophrenia symptoms who use NHS services. The first are patients with onset of their schizophrenia in earlier adult life, and now grown old. Such individuals have usually received several decades of antipsychotic drug treatment and in old age are most seriously disabled by negative symptoms with severe impairments on functional and social measures. The second group - patients with a schizophrenia-like psychosis with onset after the age of 60 years - are the subject of the **ATLAS** study. These patients present with predominantly positive psychosis symptoms, generally persecutory delusions with or without multimodal hallucinations. Symptoms are distressing and persist for many years in the absence of treatment. Very late-onset schizophrenia-like psychosis is a term that has been agreed by international consensus for onset-after-60 cases and has a prevalence of between 0.1% and 0.4% of the elderly population and an incidence of 20 new cases per 100,000 per year (Howard et al 2000) with an estimated 34,000 patients and 2,800 annual new service contacts in the UK. After dementia and depression, these patients represent the largest diagnostic group presenting to Old Age Psychiatry services. Impairments in quality of life associated with psychosis are severe and comparable to those seen in younger schizophrenia patients and elderly people with dementia. Patients often suffer the effects of their delusional beliefs for 10 or 20 years and this has a negative impact upon their families, neighbours and local social and housing services. Since increasing age beyond 60 years (Van Os et al 1995) and membership of a migrant group (Reeves et al 2001) are both risk factors for late-onset psychosis, projected changes in UK population demographics will result in more cases.

There is remarkably little good quality evidence to guide physicians' prescribing in patients with late-onset psychosis. Antipsychotic medication has established efficacy in young schizophrenia patients, and in older patients with illness onset before the age of 40 years, but no randomised placebo-controlled treatment trials have ever been conducted in the later onset clinical group. A Cochrane review (Arunpongpaisal et al 2003) identified 38 potentially relevant published trials but most had involved elderly people with chronic schizophrenia and, if patients with later onset had been included, separate outcomes for that subgroup were not reported. The single randomised study in late-onset cases (Phanjoo et al, 1990) was small (n=18) and the treatments that were compared, remoxipride and thioridazine, have subsequently been withdrawn from use. A non-randomised trial in very late-onset schizophrenia-like psychosis (Psarros et al 2009) has recently reported that five weeks of open-label treatment with amisulpiride at a mean dose of 101 mg/day (range 50-200 mg) is well tolerated and led to marked improvement in psychotic symptoms with 30% reductions in BPRS (Brief Psychiatric Rating Scale; Ventura et al 1993) and 47% reductions in total PANSS (Positive and Negative Syndrome Scale; Kay et al 1987) score.

It has generally been accepted by clinicians that antipsychotic treatment improves symptoms (Howard & Levy 1992). Expert opinion and individual clinical experience together currently guide the prescribing behaviour of psychiatrists. An influential expert consensus panel in the United States recommended treatment with risperidone at a dose of 1.6 mg per day for older patients with delusional disorder – a diagnosis sometimes used to describe very late-onset schizophrenia-like psychosis patients (Alexopoulos et al 2004). Some authors have, however, been pessimistic about treatment response rates in comparison with younger patients with psychosis (Raskind & Risse 1986). In the absence of controlled trial data, it is difficult to draw firm conclusions about this or to evaluate the potential contribution of the non-drug components of patient care, including engagement with members of the Community Mental Health Team and Social Services staff (Howard 2008). There is agreement among clinicians that patients with psychosis onset in late life can be treated successfully with much lower doses of antipsychotic (typically around 25%) than those used in younger patients

or older individuals whose psychosis began in early adult life (Howard 2008). For example, the mean dose of depot fluphenazine decanoate prescribed to patients in one naturalistic observational study was only 14.4 mg per fortnight (Howard & Levy 1992).

Typical and atypical antipsychotics are the current treatments of choice for clinicians who manage these patients. The dose ranges reported in practice (Alexopoulos et al 2004, Psarros et al 2009, Howard & Levy 1992) are comparable to those used in trials in patients with dementia and behavioural symptoms (e.g. De Deyn et al 1999) and much lower than those used in schizophrenia, suggesting that the mechanisms of both the antipsychotic effect and extrapyramidal side-effects of neuroleptics in late-onset psychosis patients may be closer to those seen in dementia than in older people with longstanding schizophrenia. Atypical antipsychotic agents in the treatment of behavioural and psychiatric symptoms in dementia have modest efficacy against aggression and agitation, with generally disappointing effects on psychosis symptoms, but this needs to be balanced against small but significant increases in mortality and stroke (Ballard & Howard 2006). A mechanism for this increased mortality has not been elucidated and it is therefore not possible to predict whether or not the same risks will apply in non-demented elderly people treated with antipsychotics.

Although antipsychotic drugs are being widely used to treat late-onset schizophrenia-like psychosis, the benefits and risks of this approach have not been properly evaluated. The Cochrane review (Arunpongpaisal et al 2003) concluded that there is no reliable clinical trial evidence upon which to base treatment guidelines for late-onset psychosis. Antipsychotic drugs may increase the risk of stroke and death and this risk needs to be balanced against potential benefits of treatment which cannot currently be quantified because of the absolute lack of any rigorous clinical trial evaluation. What is urgently needed is a large randomised trial to assess the true value of antipsychotic drugs in late-onset schizophrenia-like psychosis. The National Institute for Health Research's Health Technology Assessment programme has therefore funded **ATLAS** ("Antipsychotic Treatment of very LAte-onset Schizophrenia-like psychosis"), a placebo-controlled trial designed to evaluate whether giving a low dose of the antipsychotic drug, amisulpride, produces sufficient benefit to outweigh the potential risks. Amisulpride is used because its pharmacokinetic and cognition-sparing qualities make it appropriate for use in elderly patients (Leucht et al 2004) and because a case series has reported that amilsulpride, at a mean dose of 100 mg per day, significantly reduced psychosis symptoms in this patient group with no clinically significant adverse events (Psarros et al 2009).

For reliable results, **ATLAS** will need to randomise several hundred patients and, to make widespread participation feasible, trial procedures and documentation are kept to a minimum. Although recruiting several hundred patients will be challenging, this is a small number compared to the many tens of thousands of future patients whose treatment will be guided by the results of the **ATLAS** study.

2. TRIAL OBJECTIVES AND DESIGN

2.1. Trial Objectives

ATLAS is a multi-centre randomised controlled trial with the following objectives:

Primary Objectives

1) To determine whether amisulpride is superior to placebo in the treatment of very late-onset schizophrenia-like psychosis as measured by significant differences between amisulpride and placebo treated groups in changes in BPRS score over 12 weeks. A prior hypothesis is that benefits of amisulpride will be most apparent on the hostility, suspiciousness, hallucinations, tension, uncooperativeness and motor hyperactivity sub-scores.

2) To determine whether prolonging amisulpride for a further 24 weeks after an intial 12-week treatment period confers additional benefit, as measured by BPRS scores and by fewer patients in the amisulpride than placebo group being withdrawn to open treatment with amisulpride by their physicians?

Secondary Objectives

ATLAS will investigate:

(i) The associated risks of side-effects and serious adverse events;

(ii) Compliance with allocated treatment;

(iii) The effects of treatment on quality of life;

(iv) The cost-effectiveness of amisulpride treatment.

2.2 Trial Design

ATLAS is a pragmatic, randomised, 3-arm, double-blind placebo-controlled trial with two stages:

Stage 1 - an initial double-blind placebo-controlled stage to investigate efficacy and tolerability of oral amisulpride (groups A and B) versus placebo (group C) over 12 weeks

Stage 2 - a second double-blind stage investigating the effects of treatment continuation (group A) versus switching to placebo (group B) over a further 24 weeks.

Randomisation will be carried out centrally by the **ATLAS** Study Office (tel 0800 585323, e-mail: atlas2@ctsu.ox.ac.uk). A minimisation randomisation procedure will be used to reduce the risk of chance imbalances between arms with respect to known prognostic factors.

The ATLAS Trial: Allocations to amisulpride and placebo in Stages 1 and 2

Randomisation (3 Groups)

Stage 1 - weeks 1-12		**Stage 2 - Weeks 13-36**
(A) Amisulpride (n=100)		**Amisulpride**
(B) Amisulpride (n=100)		**Placebo**
(C) Placebo (n=100)		**Amisulpride**

2.3 Ethical considerations

The presence of significant cognitive impairment is an exclusion criterion for **ATLAS**. However, very late-onset schizophrenia-like psychosis often involves poor insight (Almeida et al 1996), with patients having difficulties in assessing their own need for treatment. Older people with psychotic illnesses participating in trials sometimes have limited understanding of trial design – particularly the use of a placebo control. Failure to understand randomisation, use of placebo control and blinding is ethically problematic (Carpenter et al 2003, Miller et al 2000, Kim 2003) – especially as participants may not recognise how these procedures might affect their treatment and care. This placebo dilemma is especially complex for conditions such as very late-onset schizophrenia-like psychosis for which existing treatments are probably more beneficial than no treatment at all but, on current knowledge, there is great uncertainty about the balance of benefits and risks. To judge whether the net benefits are sufficient to justify treatment, more reliable evidence is required on the effectiveness and side-effect profiles of antipsychotic treatment for this clinical group. However, the process of testing such agents inescapably entails clinical trials in which some patients will receive placebo treatment. Dunn

et al 2006 have highlighted the importance of three factors that contribute to how well patients with schizophrenia can be helped to understand the implications of their involvement in such research. These are: (1) the pivotal place of informed consent; (2) the capacity of patients to give informed consent (including understanding of key aspects of the protocol and an appreciation of the significance of the information provided for the individual's situation); and (3) awareness that many participants may confuse aspects of clinical care (e.g. individualisation of treatment) with those of research.

Because of the specific reasoning difficulties that this patient group have with their own assessment of treatment requirements, and the reported difficulties that older people with psychosis may have with the understanding of the randomisation and use of a placebo control in trials, the information about the trial to potential participants will be given in two stages (see section 4). A clinician who sees a patient who meets eligibility for the trial will explain the possible benefits and risks of antipsychotic treatment and briefly introduce the possibility of taking part in **ATLAS**. If the clinician considers that the patient might be interested in participating, then the patient will be given the *Patient Information* leaflet (Appendix A) and a second appointment arranged after a delay of at least 48 hours. At the second appointment, the doctor will go through the information sheet with the patient. If the clinician judges that the patient has the capacity to give informed consent, and the patient consents to take part in the trial (Appendix B), the patient's treatment will be decided by randomisation in **ATLAS**.

3. OUTCOME MEASURES

3.1 Primary Efficacy Parameter - Brief Psychiatric Rating Scale

The first primary outcome measure will be the Brief Psychiatric Rating Scale (BPRS), a widely used clinician-rated 24-item instrument for assessing positive, negative and affective symptoms in patients with psychotic disorders (Ventura et al 1993). The BPRS (Appendix C) consists of 18 symptom constructs and takes 20-30 minutes for the interview and scoring. Each item is assessed by the rater on a 7-point scale ranging from 1 (not present) to 7 (extremely severe). 0 is entered if the item is not assessed. The total score is obtained by summing the scores from the 18 items. Scores thus range from 18 to 126, with higher scores indicating greater levels of psychopathology. The BPRS will be administered at baseline, at week 4, then between weeks 10-12 and between weeks 34-36. Changes in BPRS score between baseline and the week 10-12 assessment and between the week 10-12 and week 34-36 assessments are the trial's co-primary outcomes.

The second primary outcome measure is the proportion of patients withdrawn to open treatment with amisulpride by their physicians between Weeks 13 and 36 (Stage 2) because of perceived lack of efficacy, which will be compared in participants randomised to continue amisulpride (arm A) and switch to placebo (Arm B). The difference between groups in the percentage of patients stopping trial treatment because of physician concerns about non-efficacy was used as an outcome measure in the CATIE-AD trial (Schneider et al 2003).

ATLAS uses the BPRS rather than one of the more specific schizophrenia psychopathology scales for the following reasons:

(a) The typical psychopathology of patients with very late-onset schizophrenia-like psychosis is different from that seen in schizophrenia with prominent (generally) persecutory delusions, hallucinations and hostility (Howard et al 1994). These patients characteristically do not have

affective blunting, prominent negative symptoms or formal thought disorder and although Schneiderian First Rank Symptoms are seen, these are comparatively rare. Hence the use of instruments such as the Positive and Negative Syndrome Scale (PANSS; Kay et al 1987) would not necessarily be as disease-specific or advantageous as might at first appear.

(b) The BPRS covers the important symptoms elicited in very late-onset schizophrenia-like psychosis patients, in particular the Hostility, Suspiciousness, Hallucinations, Unusual Thought Content, Tension, and Uncooperativeness items of the BPRS all assess important areas of psychopathology in these patients. The 7-point rating of the BPRS (1=not present, 2=very mild; 3=mild, 4=moderate, 5=moderately severe, 6=severe and 7=extremely severe) on each of these items generates a subscore for these six symptom domains that are primarily affected by the disorder - with pragmatic clinical relevance and meaning to clinicians - as well as an overall score and separate scores for each of the 18 domains.

(c) The BPRS has already been shown to be sensitive to improvements in symptoms associated with antipsychotic treatment in very late-onset schizophrenia-like psychosis patients. Specifically, Psarros et al (2009) reported that 5 weeks of open-label treatment with amisulpride in the same clinical group led to a 30% reduction in BPRS scores.

(d) Clinicians can be trained to achieve high levels of reliability with the BPRS within a single day. This would not be the case for instruments like the PANSS where training would take much longer and would probably not be realistic for NHS staff to undergo given their other time commitments. A review by Hedlund and Vieweg (1980) identified 10 studies of the use of the BPRS, reporting reliability coefficients of 0.80 or greater for the total psychopathology score. Inter-rater agreement for the six individual BPRS items of most interest to **ATLAS** (listed in (b) above) tends to be high with lower correlations for less relevant items such as Emotional Withdrawal and Blunted Affect. BPRS reliability can be improved and maintained by the use of brief training protocols (Schutzwohl et al 2003) and by holding regular calibration meetings to reduce rater drift (Miller and Faustman 1996). Finally, even clinically inexperienced raters can achieve over 90% levels of test-retest reliability if provided with structured interview guidance to support their use of the BPRS (Crippa et al 2001). In **ATLAS** the BPRS will be administered by a consultant old age psychiatrist or a higher trainee in old age psychiatry who is knowledgeable concerning psychotic disorders in older people, able to interpret the constructs used in the assessment and who has completed a one-day training course for the trial assessments and demonstrated good reliability on ratings of patient videos.

3.2 Secondary Efficacy Parameters

(i) **Extrapyramidal side-effects** (EPSE) measured with the Simpson-Angus Scale (SAS; Simpson and Angus, 1970). The modified SAS being used in **ATLAS** (Appendix D) measures nine extrapyramidal signs: gait, arm dropping, shoulder shaking, elbow rigidity, wrist rigidity, leg pendulousness, glabellar tap, tremor, and salivation, all of which are assessed by direct examination. The head dropping item is omitted because of difficulties with this assessment in home visits. Each item is rated on a scale of 0-4, with higher scores indicating greater severity of EPSE. The scale range is from 0-40. A standardised description is given of each item and a training video is available to optimise reliability. The scale has previously been widely used to measure EPSE within clinical trials. The SAS will be administered at baseline, 4, 10-12 and 34-36 weeks. The change in SAS in allocated groups between Baseline and Week 10-12 and between Week 10-12 and Week 34-36 will be used to assess tolerability of trial treatment.

(ii) **Compliance** expressed as percentage of prescribed trial medication taken between Weeks 1 and 12 and between Weeks 13 and 36 will be compared in patients allocated to receive amisulpride and those allocated placebo.

(iii) **Quality of life** measured with the self-rated, short, 26-item, WHO Quality of Life Scale (WHOQOL-BREF; WHO 1996, Appendix E) at Baseline, 10-12 and 34-36 weeks. The mean score of items within each domain is used to calculate domain scores for physical, psychological, social and environmental well-being, with higher scores denoting a better quality of life. Mean scores are then multiplied by 4 in order to make domain scores comparable with the scores used in the WHOQOL-100. Raw scores are then transformed into either a 4-20 or 0-100 scale for each domain. This instrument has been previously used in studies of older people with schizophrenia (e.g. Ritchie et al 2006, Klug et al 2008) and psychosis patients in residential care settings (Picardi et al 2006).

(iv) **Cost-effectiveness** calculated by attaching nationally applicable unit cost measures to health and social service use and medication data collected with a modified version of the Client Service Receipt Inventory (CSRI; Beecham and Knapp 2001, Appendix F) and the EQ-5D (EuroQol Group 1990, Appendix G) for each patient at baseline, 10-12 and 34-36 weeks. We will also collect data on informal carer inputs, and attach imputed values.

We will investigate the cost-effectiveness of oral amisulpride versus placebo over 12 weeks and the cost-effectiveness of treatment continuation for a further 24 weeks versus discontinuing amisulpride treatment at 12 weeks. We will calculate differences between patient groups in the change in BPRS score over 12 weeks and then over a further 24 weeks; calculate costs for each Stage (covering health and social care service use, medication and carer support). For each Stage an incremental cost-effectiveness ratio will be computed, and a cost-effectiveness acceptability curve (CEAC) plotted. The CEAC will be generated from the net benefit approach using bootstrap regression for a range of hypothesised values for willingness to pay for incremental improvements in psychiatric symptoms measured on the BPRS. Each cost-effectiveness analysis will be conducted from the perspective of (a) the NHS and social services, and (b) society as a whole, the main difference being the exclusion of formal and informal carer costs and out-of-pocket patient or carer payments from (a). We will also examine cost-effectiveness using QALYs computed from EQ-5D and by cross-walking from BPRS scores (using evidence on the links between BPRS and EQ-5D gleaned from other studies).

4. PATIENT ENTRY

4.1 Screening for eligibility

Participants will be patients with very late-onset schizophrenia-like psychosis recruited from the community and inpatient teams of UK Old Age Psychiatry services. Initial assessments can take place either in the patient's place of residence or in a clinic setting. At the first appointment, patients potentially meeting the diagnostic criteria for very late onset schizophrenia-like psychosis will be assessed (diagnosis, MMSE, BPRS, eligibility and exclusion criteria).

Eligibility criteria:

(i) Diagnosis of very late-onset schizophrenia-like psychosis (defined by International Consensus Group criteria, Howard et al 2000), including onset of delusions and/or hallucinations after the age of 60 years; and

(ii) BPRS score ≥30; and

(iii) Capacity to give informed consent to inclusion in trial (in the view of the responsible clinician).

Exclusion criteria:

(i) Evidence of significant cognitive impairment and MMSE score <25.

(ii) Uncontrolled serious concomitant physical illness.

(iii) Primary diagnosis of affective disorder.

(iv) Prescribed amisulpride in previous 28 days. (Patients who have been treated with other antipsychotic agents in the previous 28 days but still satisfy the eligibility criteria can participate and this will be included as a stratification factor at randomisation).

(iv) Contraindication to amisulpride (e.g. phaeochromocytoma, prolactin dependent tumour or potential drug interactions: e.g. with levodopa - see most recent Summary of Product Characteristics http://emc.medicines.org.uk/).

(v) Participation in another Clinical Trial of an Investigational Medicinal Product (IMP) in the previous 28 days.

Patients who meet the eligibility criteria should have the potential benefits and risks of antipsychotic treatment explained with taking part in the **ATLAS** study introduced as one possible option. Patients who are potentially interested in taking part in the study should be given a patient information leaflet (Appendix A) to find out more about the study before deciding whether or not to participate. A second appointment should be arranged in the clinic or the patient's home, after a delay of at least 48 hours, to discuss the trial information and seek the patient's consent to participate. Once a potentially eligible patient is identified, the **ATLAS** Study Office should be informed (see registration information, Appendix H) and, if not already supplied, an **ATLAS** patient treatment pack will be sent to the hospital pharmacy within two working days so that treatment can be given to the patient at, or following, the second appointment if they consent to be randomised (see section 4.3 Randomisation).

4.2 Information and consent visit

The clinician will discuss the **ATLAS** study in detail with the patient at the second clinic appointment. The patient should be given a general outline of the three possible options: choice of treatment, randomisation into the 3-arm trial, more time to consider. A checklist is provided in the **ATLAS** study folder to facilitate this information appointment. After a full explanation has been given of the treatment options, and the manner of treatment allocation, all suitable patients should be invited to take part in the randomised component of the trial, but it is essential not to put undue pressure on the patient. Written, informed consent will be sought from those agreeing to take part in **ATLAS** (Appendix B). If the patient is dependent on a carer, assent should also be obtained from the carer using the carer assent form in the study folder. After obtaining consent, the psychiatrist or nurse should undertake the remaining baseline assessments (WHOQoL-BREF, CSRI) and the patient examined using the SAS. The BPRS does not need to be repeated as the eligibility BPRS will be used as the study baseline. After completion of all baseline assessments, patients will be randomly allocated (see below). If the patient declines to take part, the **ATLAS** Study Office should be notified so they know that the treatment pack has not been obtained from the hospital pharmacy. Reasons why eligible patients are not invited, or do not consent to take part, should be recorded on the screening log in the **ATLAS** study folder.

4.3 Randomisation: amilsulpride or placebo from ATLAS treatment pack

After informed consent and completion of baseline assessments, randomisation will be carried out centrally by the **ATLAS** Study Office (tel 0800 585323). The person randomising will need to answer **all** of the telephone questions and should complete the **ATLAS** randomisation notepad (Appendix H) before calling to help in preparing for them. Alternatively, randomisation forms may be faxed or scanned and e-mailed to the **ATLAS** study office (fax TBC, e-mail: atlas2@ctsu.ox.ac.uk) who will call back with a treatment allocation. After **all** the necessary details have been provided, the allocated treatment pack number will be specified. The recruiting PI (or other medically qualified doctor with a substantive or honorary contract with the recruiting NHS Trust and who has signed the 'Recruiting Investigator site delegation of authority form') should complete an **ATLAS** prescription form (provided in the study folder). The first **ATLAS** treatment pack with this number, which will contain the initial 12 weeks' treatment, should be obtained from the hospital pharmacy and given to the patient. Instructions for the trial treatments are available on a label which can be stuck in the patient's clinical notes. The baseline assessments should be labelled with the patient's treatment pack number and posted to the **ATLAS** Study Office in the Freepost envelopes provided in the study folder. The patient's GP should be notified that they are in **ATLAS** and a specimen "Letter to GP" is provided for this purpose (Appendix I).

5. TREATMENT AND FOLLOW-UP PROCEDURES

5.1 Trial treatment

Trial treatment will be oral amisulpride or identically appearing placebo packed into treatment cartons of 12 weeks' treatment in the form of 3 x 28 blister-packed capsules (for Stage 1) or 24 weeks' treatment in the form of 6 x 28 blister-packed capsules (for Stage 2). Trial treatment will be packed, labelled, QP released and dispatched to participating centres' pharmacies by Bilcare GCS (Europe) Ltd. As described above, patients will be allocated a treatment pack number following randomisation and the initial 12-week Stage 1 treatment carton obtained from the hospital pharmacy. Treatment should start as soon as possible and should be continued for thirty-six weeks unless a definite contra-indication is thought to have developed. If the patient is still compliant with treatment at the 10-12 week assessment, the **ATLAS** Study Office should be informed (tel 0800 585323) and the second **ATLAS** Stage 2 treatment carton, with the patient's unique identifying number, will be allocated. This carton, which will contain the patient's treatment for weeks 13 to 36 in the form of 6 x 28 blister-packed capsules (a total of 24 weeks treatment at one capsule a day), should again be obtained from the hospital pharmacy, using an **ATLAS** prescription form, and given to the patient. Pharmacy departments in each site will maintain a study medication dispensing log, including date dispensed, batch number, expiry date, and number of capsules dispensed. The study specific prescriptions will be maintained in the pharmacy file for audit purposes.

The dosing regimens for the three treatment arms are:

Group (A) will take one capsule containing 100mg amisulpride orally per day for a period of 36 weeks

Group (B) will take one capsule containing 100mg amisulpride orally per day for a period of 12 weeks, followed by one matching placebo capsule orally per day for a further 24 weeks.

Group (C) will take one placebo capsule orally per day for a period of 12 weeks, followed by one capsule containing 100mg amisulpride orally per day for a further 24 weeks.

Treatment compliance will be monitored by capsule count. Patients should be asked to bring any unused study medication at each follow-up visit and at the end of the trial. The local PI or research worker will keep a log of study medication returns, return date and amount of study medication returned and enter the information on the patient follow-up form (Appendix J). Once returned medication has been logged, it should be destroyed by the local pharmacy.

Arrangements for continued treatment at the end of the trial will be made on an individual patient basis by the Local Investigator or other clinicians responsible for the patient's care at this point. Responsible clinicians will be telephoned 28 days after completion of the last trial assessment to confirm that a treatment plan is in place for the individual patient. On present evidence, no recommendation can be made about treatment beyond 36 weeks but the Data Monitoring Committee (see section 8.4) will scrutinise the accumulating data from **ATLAS** and, if clear evidence for or against amisulpride treatment emerges, will notify the Steering Committee who will then make appropriate recommendations.

5.2 Randomisation code break

All Investigators and patients will remain blinded to the treatment allocation throughout the trial. Unblinding should not normally be necessary as serious side-effects should be dealt with on the assumption that the patient is on active amisulpride treatment. Where possible, study medication should be omitted rather than unblinded. If considered definitely necessary for patient management, the randomisation service can be telephoned to unblind trial treatments (0800 585323). The medical reason for unblinding must be provided.

5.3 Other treatments

Treatment with other typical or atypical antipsychotic drugs is not allowed during the study period. Patients who are being prescribed other antipsychotic medication at entry to the trial should cease before starting **ATLAS** treatment. Also, when prescribing concomitant medication, investigators should take into consideration the potential for drug interactions – e.g. with levodopa - as described in the most recent Summary of Product Characteristics; see http://emc.medicines.org.uk/. Apart from this, giving out the trial treatments and undertaking the follow–up assessments, all other aspects of patient management are entirely at the discretion of the local doctors. Patients are managed in whatever way appears best for them, with no special treatments, no laboratory or other special investigations, and no extra follow-up required. Concomitant medications should, however, be recorded on the **ATLAS** patient follow-up form (Appendix J).

5.4 Assessments at 4, 10-12 and 34-36 weeks

Assessments will be undertaken prior to randomisation and then at week 4, between weeks 10-12 and between weeks 34-36 (see flowchart below). The latter two follow-up visits are scheduled in the last two weeks before completion of the treatment phase to ensure that the patient is still taking trial treatment at the assessment even if their appointment is delayed for any reason. Follow-up assessments should be undertaken whether or not patients remain compliant with trial treatment.

ATLAS Study Flowchart

	Eligibility screening	*Information & consent*	Week 4	Week 10-12	Week 34-36
Diagnosis (ICC criteria)	X				
MMSE	X				
BPRS	X		X	X	X
Inclusion Criteria	X				
Exclusion Criteria	X				
Capacity Assessment	X	X			
Patient registration	X				
Informed Consent		X			
Randomisation		X			
Simpson Angus Scale		X	X	X	X
EuroQol EQ-5D		X		X	X
WHO QoL Brief Scale		X		X	X
Client Service Receipt Inventory		X		X	X
Dispense Medication		X		X	
Compliance Check			X	X	X
Adverse Events			X	X	X

5.4 Minimising loss to follow-up

The trial aims to minimise the number of patients who discontinue treatment and, especially, the numbers with missing follow-up assessments. However, in some circumstances discontinuation may occur and can be initiated by the patient, their carers, investigators or other responsible physicians.

Discontinuation from treatment only

Patients or their doctors commonly choose to discontinue clinical trial medication for the following reasons:

(i) Patient withdraws consent to further treatment.
(ii) Intercurrent illness or side-effects preventing further treatment.
(iii) Any change (or lack of change) in the patient's condition justifying discontinuation of treatment in the clinician's opinion.

Most patients who discontinue treatment are happy to continue to be followed up. In this case **ATLAS** outcome data should be collected in accordance with the protocol. The reason for stopping **ATLAS** treatment (e.g. side-effects, lack of perceived effectiveness, patient choice or other) and the use of other treatment (if any) should be recorded on the patient follow-up form (Appendix J). Unused drugs should be destroyed (see section 5.1) except that, if patients discontinue treatment in the first 12 weeks, the 13-36 week treatment pack should remain in the pharmacy from where it may be re-allocated to another trial patient.

Discontinuation from treatment and follow-up assessments

Patients may choose to discontinue both treatment and study assessments. In this case the local PI or research worker should attempt to ascertain the reason for a patient's discontinuation of follow-up assessments, without compromising their right to withdraw at any time without giving a reason, and record this on the patient follow-up form (Appendix J). Note that, unless the patient specifically revokes their earlier consent for information about their progress to be sent to the **ATLAS** Study office, clinical information will continue to be collected and patient information will be retained in the trial database and used for intention-to-treat analyses of study outcome.

Loss to follow-up

Loss to follow-up will be minimised by all available means, including use of centrally held NHS records, and will be monitored both locally and centrally. A patient will only be regarded as lost to follow-up with the agreement of the recruiting PI and the trial manager.

Patient transfers

For patients moving from the area, or to another doctor or hospital, every effort should be made for the patient to be followed up and for this other centre to take over responsibility for the patient assessments. A copy of the patient's study documentation will need to be sent to the new site, the patient will have to sign a new consent form and, until this occurs, the patient remains the responsibility of the original centre. The **ATLAS** Study office can help facilitate this process.

5.6 Expected duration of trial

From the regulatory perspective, the end of the trial is defined as the end of the interventional phase, 36 weeks after the final patient is randomised. Completion for an individual patient is defined as completion of 36 weeks on the trial medication or discontinuation of follow-up for any reason. The trial may, however, be stopped earlier by the Trial Steering Committee if the Independent Data Monitoring Committee, in accordance with the IDMC charter, recommend to the Trial Steering Committee that the trial be stopped. The criteria for stopping the trial will be established as part of standard operating procedures of the IDMC (see section 8.4) at their first meeting.

6. SAFETY MONITORING PROCEDURES

6.1 Specification, Timing and Recording of Safety Parameters

Safety will be assessed at the 4, 10-12 and 34-36 week visits via a face to face interview with the researcher who will systematically enquire about changes in the subject's health state between assessments. Patients will also be examined and rated on the modified Simpson-Angus Scale (Appendix D) to detect and quantify the development of extra-pyramidal side-effets (EPSE).

6.2 Procedures for Recording and Reporting Adverse Events

The Medicines for Human Use (Clinical Trials) Regulations 2004 and Amended Regulations 2006 gives the following definitions:

Adverse Event (AE): Any untoward medical occurrence in a subject to whom a medicinal product has been administered including occurrences which are not necessarily caused by or related to that product.

Adverse Reaction (AR): Any untoward and unintended response in a subject to an investigational medicinal product which is related to any dose administered to that subject.

Unexpected Adverse Reaction (UAR): An adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question set out in the summary of product characteristics (SPC) for that product (for products with a marketing authorisation) – available at http://emc.medicines.org.uk/ - or the Investigator's Brochure (IB) relating to the trial in question (for any other investigational product).

Serious Adverse Event (SAE), **Serious Adverse Reaction (SAR)** or **Unexpected Serious Adverse Reaction**: Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that:

1. Results in death;
2. Is life-threatening;
3. Requires hospitalisation or prolongation of existing hospitalisation;
4. Results in persistent or significant disability or incapacity;
5. Consists of a congenital anomaly or birth defect.

A **Suspected Unexpected Serious Adverse Reaction** is usually referred to as a **SUSAR** and requires expedited reporting (see below).

Note the term "severe" is often used to describe the intensity (severity) of a specific event. This is not the same as "serious," which is based on patient/event outcome or action criteria.

Assessment of Causality

The relationship between study drug and the adverse event will be assessed by the local PI and categorised using clinical judgement into one of the following five categories:

1. ***Not related*** – temporal relationship not reasonable or event explained in isolation by another cause
2. ***Unlikely related*** – temporal relationship unlikely or event likely to be explained by another cause
3. ***Possibly related*** – temporal relationship is reasonable but event could be due to another equally likely cause
4. ***Likely related*** – temporal association is reasonable and event is more likely to be due to study drug than other cause
5. ***Definitely related*** – temporal relationship is reasonable and there is no other cause to explain event, or re-challenge is positive

For classification of causality ***possible, likely*** *and* ***definite*** categories should be considered as reactions in the **ATLAS** trial.

Reporting Responsibilities

King's College London, as Sponsor, have delegated the delivery of the Sponsor's responsibility for Pharmacovigilance - as defined in Regulation 5 of the Medicines for Human Use (Clinical Trials) Regulations 2004 - to the Joint Clinical Trials Office (JCTO).

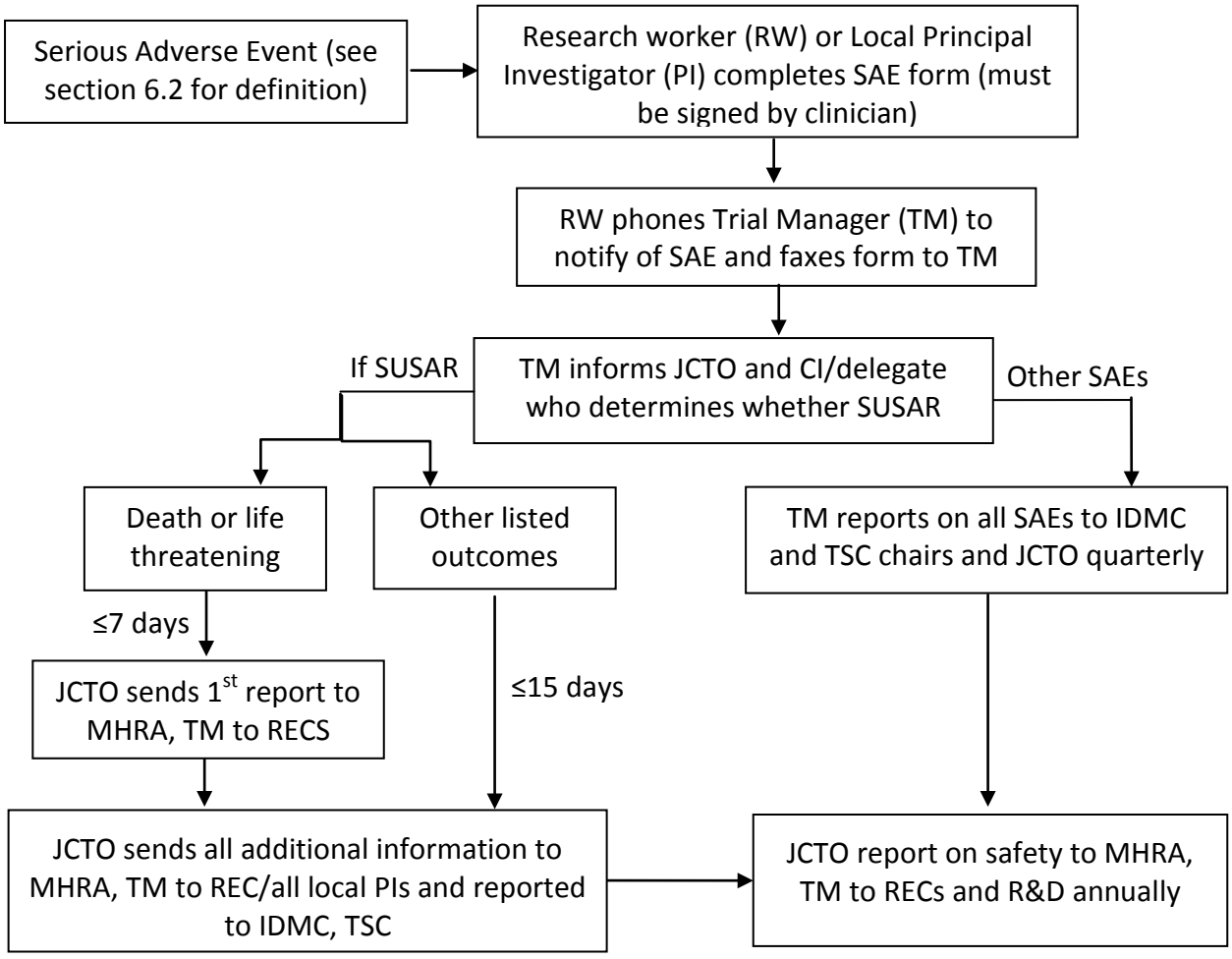
All SAEs, SARs and SUSARs (excepting those specified in this protocol as not requiring reporting) will be reported immediately to the JCTO and Chief Investigator by the **ATLAS** Trial Manager in accordance with the current Pharmacovigilance Policy. The CI, or delegate, will review these events to determine whether they are SUSARS needing expedited reporting. In addition, all AEs, serious or otherwise will be recorded and reviewed by **ATLAS**'s independent Data Monitoring Committee at regular intervals.

The JCTO will report SUSARs to the MHRA. The Chief Investigator will delegate responsibility to the **ATLAS** Study Office at CTSU for reporting SUSARs and other SARs to the relevant ethics committees, PIs and R&D departments.

Reporting timelines are as follows:

- SUSARs that are fatal or life-threatening must be reported not later than 7 days after the Sponsor is first aware of the reaction. Any additional relevant information must be reported within a further 8 days.
- SUSARs that are not fatal or life-threatening must be reported within 15 days of the Sponsor first becoming aware of the reaction.
- The Chief Investigator will provide an annual report of all SARs (expected and unexpected) and SAEs which will be distributed to the Sponsor (through JCTO), MHRA and the REC.

Reporting Flowchart for SAEs, SARs and SUSARs



7. SIZE, STATISTICS AND DATA MONITORING PROCEDURES

7.1 Sample Size

Patients with very late-onset schizophrenia-like psychosis have very rarely been recruited to randomised controlled trials but, for reasons outlined in this proposal, the conduct of such a trial is an important priority. Because of uncertainties with regard to recruitment and drop-out rates, the trial design will be adaptive with two phases. An initial Feasibility Phase of 100 patients, leading to a Full Study Phase if recruitment and retention milestones are achieved. The target will be to recruit 100 patients in 18 months and to achieve over 70% compliance with the first 12 weeks of treatment. The statistical power calculations will be reviewed by the **ATLAS** TSC in the light of information from the Feasibility Phase – in particular recruitment and compliance rates. A pragmatic decision will then be made on the final recruitment figure target. The sample size calculations provided here are thus estimates not immutable figures.

The minimal clinically relevant difference (MRD), given the established hazards of antipsychotic drugs, is considered to be 5 points on the BPRS. Since Psarros et al (2009) reported a mean 14-point BPRS improvement over 5 weeks of treatment in an open-label trial, an anticipated treatment effect of at least 5 points is plausible. From these same data, we estimate that the standard deviation of BPRS scores will be 9 BPRS points. We are thus powering the trial on a minimal worthwhile standardised effect size of 0.55 (=5/9) standard deviations, a moderate treatment effect (Cohen, 1988, Norman et al 2003).

Our initial aim will be to recruit 300 patients. Even allowing for a 25% drop-out rate by 36 weeks, i.e. 225 of 300 with outcome assessments (75 patients in group A allocated 12 weeks amisulpride then 24 weeks further amisulpride vs. 75 patients in group B allocated 12 weeks amisulpride then 24 further weeks of placebo completing study assessments), **ATLAS** will have greater than 90% power at $2p<0.05$ to detect the MRD of 5 points (0.55sd) between those continuing and stopping in Stage 2. There will be even greater statistical power (90% at $2p<0.01$) to detect the MRD at 4 or 12 weeks during Stage 1, even with a drop-out rate as high as 25% by 12 weeks (150 patients in groups A and B receiving 12 weeks amisulpride vs. 75 patients in group C receiving 12 weeks placebo).

If, following the Feasibility Phase, a 300 patient recruitment target seems unrealistic then a smaller study should still prove to have enough power. For example, if only 200 patients are recruited in total with 20% drop-out by 36 weeks, then the study will still have 90% power at $2p<0.05$ to detect the MRD at 12 weeks and 80% power at $2p<0.05$ to detect the MRD at 36 weeks. It should be noted that these power calculations are conservative in that the principal repeated measures analysis will provide additional statistical power by using all available data (Frison & Pocock, 1992) and because drop-out from treatment will be informative (i.e. a treatment failure) and sensitivity analyses will be undertaken imputing missing outcome assessments, which will also enhance statistical power.

Randomisation will be obtained by telephone, fax or internet from the **ATLAS** Study office. A minimised randomisation procedure will be used to ensure balance of treatment allocation overall and by the following variables to be used in the pre-specified sub-group analyses:

- **a.** Age (60-69, 70-79, 80+ years)
- **b.** Gender
- **c.** Home circumstances (Living with spouse/partner, living alone, other)
- **d.** BPRS score (30-39, 40-49, 50+)
- **e.** Time since onset of symptoms (<6 months, ≥6 months)
- **f.** Previous antipsychotic treatment (No, Yes >1 month previously, Yes ≤28 days ago)

7.2 Analysis

The trial will comprise two stages (see Flow Diagram, section 2.2). Stage 1 lasts from weeks 1-12 inclusive. Stage 2 lasts from weeks 13-36.

Patients will be randomised between three arms:

(A) Amisulpride 100mg Stage 1 then Amisulpride 100mg Stage 2

(B) Amisulpride 100mg Stage 1 then Placebo Stage 2.

(C) Placebo Stage 1 then Amisulpride 100mg Stage 2.

The main analysis will be undertaken once all patients have reached 36 weeks from randomisation. To assess efficacy of 12 weeks of amisulpride treatment in Stage 1, the primary outcome of the BPRS will be compared using a repeated measures model. Data from 4 weeks and 12 weeks will be the outcome variables and baseline scores will be entered into the model as a covariate. The comparison will be between active amisulpride treatment (i.e. Arms A and B of the trial grouped together) and placebo (Arm C). This will be an Intention-To-Treat (ITT) analysis – all patients who are randomised and take at least one capsule of their treatment will be included in the comparison, analysed according to their randomised allocation, including patients who discontinue **ATLAS** trial treatment and switch to open amisulpride treatment. Wherever possible, we will continue to collect follow-up data from these patients after they move to open-label treatment, so that the dataset will be as complete as possible.

To assess the value of continuing treatment in Stage 2, Arm A (amisulpride – amisulpride) will be compared with Arm B (amisulpride – placebo). There is only one outcome time point (36 weeks), and so an analysis of covariance will be carried out, again entering the "baseline" (which here will be the 12 week scores) into the model as a covariate. This analysis will again be ITT, except that patients who withdraw from protocol treatment in Stage 1 – and hence do not receive treatment packs after week 12 – will not be included in the Stage 2 comparison. This will not introduce bias: the two arms receive the same treatment regimen in Stage 1 and since neither patients nor their doctors in this double-blind trial will be aware which treatment they would receive in Stage 2, this can not influence the decision to withdraw and, consequently, result in systematic differences between Arms A and B during Stage 2. Thus, excluding patients who do not reach stage 2 will not introduce selection bias to the comparison at Stage 2.

Other continuous outcome measures will be analysed by similar methods. Exploratory analyses will be undertaken, using standard tests for interaction, of any differential treatment efficacy in subgroups of patients defined by the randomisation stratification variables. Such subgroup analyses will be interpreted appropriately cautiously. Treatment discontinuation rates will be compared using a chi-squared test, or the logrank test if possible (i.e. if accurate data on time of discontinuation can be obtained). Reasons for stopping treatment will be collected and, since stopping **ATLAS** treatment is likely to be informative (e.g. a failure of treatment), this information will be used in sensitivity analyses to investigate and reduce the impact of missing data.

8. ORGANISATION

To ensure the smooth running of **ATLAS** and to minimise the overall procedural workload, it is proposed that each centre should designate individuals who would be chiefly responsible for local coordination of clinical and administrative aspects of **ATLAS**. The **ATLAS** Study Office, working together with MHRN networks, will provide as much assistance as they can to local co-ordinators and investigators in obtaining Trust approval in each centre and helping resolve any local problems that may be encountered.

8.1 Local Principal Investigator

Each Centre should nominate one person to act as the Local Principal Investigator (PI). Their responsibilities will include:

1. **Liaising with local GPs, nurses, social services and Clinical Research Networks** The PI will need to liaise with all who refer patients to the centre to encourage them to consider suitable patients for **ATLAS**. Local procedures will need to be developed to ensure assessment and discussion of individual patients' suitability for **ATLAS** at Team meetings, providing eligible patients with **ATLAS** information sheets, arranging appointments to discuss taking part in the study, obtaining consent and randomisation, and delivering allocated drug packs to patients. Any member of the clinical team can obtain consent and randomise patients although it is obviously essential that teams liaise closely to agree who randomises and which patients are suitable for **ATLAS**.
2. **To ensure that all medical and nursing staff involved in the care of very late-onset schizophrenia-like psychosis are reasonably well informed about the study** This involves distributing the **ATLAS** materials to all relevant staff, displaying the wall-chart where it is likely to be read, and distributing the **ATLAS** newsletters. A regularly updated PowerPoint presentation will be provided to centres so that they can be shown from time to time, especially to new staff.
3. **To ensure compliance with research governance requirements** This involves obtaining management approval for **ATLAS**, ensuring that all members of the clinical team are familiar with the protocol and trial procedures, in particular serious adverse event reporting, maintaining the Local Study Site File with copies of trial materials, approval documents, consent forms and any other required documents as advised by the **ATLAS** Study office.

8.2 Local Study Coordinator at each centre

It is suggested that each Centre should designate one person as Local Study Coordinator. This role might suit a higher trainee in old age psychiatry or, if available, a research nure. The Local Study Coordinator would be responsible for ensuring that all eligible patients are considered for **ATLAS**, that patients are provided with **ATLAS** information sheets and have an opportunity to discuss the study as required, registering patients to ensure that **ATLAS** drug packs are available when potential patients are identified, obtaining consent, randomisation, obtaining drug packs from the pharmacy when patients are randomised, given to the patient with treatment instructions, and follow-up assessments are undertaken as scheduled in the protocol. The **ATLAS** Local Study Coordinator will also ensure that **ATLAS** trial forms, questionnaires are completed and treatments are administered as scheduled (unless some contraindication develops). Again, this person would be sent updates and newsletters, would be invited to **ATLAS** progress meetings and appropriately credited in study reports..

8.3 Trial Steering Committee

The TSC is responsible for the independent supervision of the scientific and ethical conduct of the trial on behalf of the Trial Sponsor and funding bodies. The TSC will review data, blinded to study treatment, on progress of the trial, including recruitment, protocol adherence, serious adverse events, and will determine the future progress of the trial in light of regular reports from the DMEC and Trial Management Group (TMG). The TSC has the power to prematurely close the trial. The TSC will meet annually or more often if the chair determines a reason for doing so. In addition to the independent voting members (listed inside front cover), the TSC will include the **ATLAS** Chief Investigator, Trial Manager and Statistician, and representatives from the funding body and Sponsor.

8.4 Data Monitoring and Ethics Committee

The independent Data Monitoring and Ethics Committee (DMEC - members listed inside front cover) is responsible for monitoring the unblinded accumulating data from the trial including: protocol adherence, serious adverse events and side effects of treatment as well as the difference between the trial treatments on the primary and secondary outcome measures. Based on the unblinded interim analyses, the DMEC can recommend protocol modifications to the TSC, including premature closure of the trial. The DMEC will agree their structure, organisation and stopping rules in a DMEC Charter (DAMOCLES Study Group, 2005) at their first meeting. The DMEC will meet annually or more often if the chair determines a reason for doing so. The chief investigator (or their representative) and the trial manager will be in attendance for the open session of the DMEC meeting. The trial statistician will be in attendance for the open session and to present and answer any questions on the interim analyses in the closed session. There will then be a session of just the independent members to agree any actions needed and the content of the DMEC report to the Trial Steering Committee.

8.5 Ethics & Regulatory Approvals

The trial will be conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of GCP and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework and the Medicines for Human Use (Clinical Trial) Regulations 2004, as amended in 2006 and any subsequent amendments.

This protocol and related documents have been reviewed and approved by:

(1) The London and Surrey Borders Multicentre Research Ethics Committee (REC).

(2) The Medicines and Healthcare products Regulatory Agency (MHRA) for Clinical Trial Authorisation.

The integrated form for both site-specific assessment (SSA) and R&D approval at all participating NHS sites will also be approved prior to recruitment at each site. Annual progress and safety reports and a final report at conclusion of the trial will be submitted to the REC and the MHRA within the timelines defined in the Regulations.

8.6 Quality Assurance

Recruitment to **ATLAS** and the conduct of trial assessments will be undertaken by senior NHS clinicians who are experienced in the assessment and rating of psychopathology. All Investigators and staff employed on the grant will be trained in GCP, use of the assessment tools and trial guidance. Wherever possible, the same rater will be used for all baseline and follow-up ratings on each individual patient. All raters will have undergone a video-based training protocol and demonstrated reliability of >0.80 on their ratings of example videos of patients during the locally delivered training

day before they are able to recruit to the trial. Finally, all raters will undergo mandatory repeat BPRS rating training to reduce rater drift at which point the reliability of their ratings will be re-assessed against standardised training videos. Any rater whose reliability has dropped below 0.80 will have to repeat the initial training protocol and demonstrate a reliability of >0.80 before they recruit further participants to **ATLAS**.

The Trial Manager will maintain a Trial Master File containing the essential trial documents in accordance with GCP and the EU Clinical Trial Directive. In addition, each site will be provided with an Investigator Site File and a Pharmacy File, which will contain the essential trial documents.

The trial will be carried out in accordance with this protocol and the Sponsor's Standard Operating Procedures (SOPs). Trial specific functions will be conducted in accordance with these and will ensure the procedures within the trial are carried out in the same way in each centre.

Monitoring of this trial to ensure compliance with the protocol and Good Clinical Practice will be managed and overseen by the Joint Clinical Trials Office Quality Team, in accordance with JCTO SOPs, on behalf of the Sponsor. Each site will take part in a site initiation, to ensure appropriate staff training, resources, IMP management and essential documents are in place. During the course of the trial the study file will be reviewed for appropriate documentation of patient consent and participation in the trial, and a sample of data will be verified against patient notes in accordance with the risk assessment and monitoring plan for the trial. The Investigator(s) will provide direct access to source data and other documents (e.g. patients' case sheets, etc) to permit trial-related monitoring, audits, REC review, and regulatory inspections (where appropriate). At the end of the trial each site will be formally closed down once trial activity at the site has ceased.

8.7 Data Handling

The Chief Investigator will act as custodian for the trial data. All trial data will be stored on a password-protected computer and archived in line with the Medicines for Human Use (Clinical Trials) Amended Regulations 2006 as defined in the Joint Clinical Trials Office Archiving Standard Operating Procedure (SOP).

8.8 Publication Policy

The results of the study will be reported and disseminated at international conferences and in peer-reviewed scientific journals. A meeting of the Trial Steering Committee and **ATLAS** collaborators will be held after the end of the study to allow discussion of the main results prior to publication. The success of **ATLAS** depends entirely on the wholehearted collaboration of a large number of doctors, nurses and others. For this reason, chief credit for the main results will be given not to the committees or central organisers but to all those who have significantly contributed to the study. All grant holders and members of trial committees together with anyone who during the course of the study enters two or more patients into the study and research workers at these centres who have been involved with the trial for more than 12 months would have authorship rights as part of the **ATLAS** Trialists Group. Presentations or publications pertaining to the **ATLAS** trial must not be made without the prior agreement of the Trial Management Group.

8.9 Financial Aspects

Funding to conduct the **ATLAS** trial is provided by the Department of Health's Health Technology Assessment programme (reference number 09/55/06). The duration of the grant is from October 2011 to February 2016. The grant will be administered by King's College London and sub-contracts will be drawn up for the Study Office at CTSU, University of Oxford and for other sites.

9 Signatures

Chief Investigator

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_____ _____

Chief Investigator Date

Print name

_____ _____

Principal Investigator at site Date

Print name

APPENDIX A – Patient information sheet

To be printed on local trust headed paper

ATLAS - Antipsychotic Treatment of LAte-onset Schizophrenia-like psychosis

Patient Information Sheet

Version 1.0, 17/07/2011

We would like to invite you to take part in a medical research study called **ATLAS**. The aim of this study is to find out the best way to treat people with symptoms like yours. Before deciding whether to take part, it is important for you to understand why the **ATLAS** study is being undertaken and what it would involve if you do decide to take part. Please take time to read this information carefully and ask us if anything is not clear or if you would like more information. Feel free to talk to others about the research project if that would help you decide whether you want to be involved. You can take a copy of this information sheet to help these discussions.

1. What is the ATLAS Study?

Psychiatrists don't really know whether prescribing a medicine will help people with difficulties like those you are having. If medicine does help, we are not sure which patients should be treated. The **ATLAS** study is being undertaken to see if one widely used medicine called amisulpride is effective in helping people with symptoms like yours. **ATLAS** is what is called a 'clinical trial' where people taking part are prescribed either amisulpride or no amilsulpride. This is the standard way of comparing treatments and it is the most reliable way to tell how effective this drug is.

2. Why am I being asked to take part In ATLAS?

The doctors and nurses looking after you think that you may be suitable for the **ATLAS** study because of the symptoms that are currently causing you difficulties. We know that amisulpride is effective in treating the symptoms of people with a condition called schizophrenia that usually affects younger people and is similar but has more severe symptoms than yours. We think that a low dose of amisulpride might help people with symptoms like yours but we can't be sure yet, which is why we are inviting you to take part in this research study.

3. Do I have to take part?

No. Taking part in research is always voluntary. It is up to you to decide whether or not you want to take part. If you decide not to, you do not have to give any reason, nobody will think badly about you and this will not affect the quality of the care you will receive from your clinical team.

4. What would taking part involve for me?

If you do decide to take part you will be asked a series of questions about your health and the problems you have been having. You will be asked to take a pill each day for 36 weeks that would contain either the study medication (amisulpride) or a placebo. A placebo is a 'dummy medicine'; it looks and tastes just like real amisulpride but it has no real drug inside it. The reason we need to include a placebo treatment is because we don't want you to know which treatment you are taking because this could influence the way you report your symptoms or side-effects at clinic visits. Again, this is the standard and most reliable way of comparing treatments.

There are three treatment groups in **ATLAS**: the first receives amisulpride throughout the 36-week study, the second receives 12 weeks of amisulpride then 24 weeks of placebo, and the third 12 weeks of placebo then 24 weeks of amisulpride. Thus, all patients receive amisulpride at some stage of the trial. The decision as to which treatment group a patient is in is made by a process called randomisation, which is like a lottery draw with an equal chance of being in each group. This ensures a fair comparison between the different treatments. Neither you, your doctor, nor any of the study team will know whether you are taking amisulpride or placebo medicine.

If you do take part in **ATLAS**, the researchers will ask you the same questions about your health about 4 weeks, 10 weeks and 36 weeks after you enter the study.

5. What are the possible benefits of taking part?

Your symptoms may improve because of the medication that you are asked to take or they may improve simply as a result of the care, monitoring and assessment that you receive through your involvement in the study. The main benefit of you taking part, though, is for future patients with problems like yours as the results of this research will help doctors treat these people better in the future.

6. What are the possible risks of taking part?

The main risks from taking part in the **ATLAS** study are that you may develop side effects from treatment or your symptoms may get worse. The side-effects that have been reported by some patients taking amisulpride in the past are nausea, difficulty sleeping, a feeling of restlessness and weight gain. These side-effects are seen less often with amisulpride than with other similar drugs and are also less likely with the low dose of amisulpride that we are using in **ATLAS**. If you do have troublesome symptoms, or for any other reason, you can decide at any time not to continue with study treatment. An important aim of the study, though, is to find out how many patients complete their treatment and how people get on if they stop taking treatment. For this reason, we would still like to ask people who stop treatment the same questions about their health and use the information about how their treatment affected them in the final study analysis. But, again, you do not have to

continue in the study, or give any reason if you decide not to, and this would not affect the quality of your clinical care.

If you are already taking a drug like amisulpride at the point where you enter the study, there is a 1 in 3 chance that you will be allocated treatment with an inactive placebo during part of the trial. If your previous treatment had been helping you, it is possible that changing to placebo might make your symptoms a little bit worse. Your doctor will be seeing you regularly during the study and will be checking to see what symptoms you have. Also, if you feel that your symptoms have got worse and you want to stop the trial medication and return to the tablets you were taking initially you are able to do so at any point.

7. Will my taking part in the research study be kept confidential?

Yes. All information about your involvement with the research study will be kept strictly confidential in the same way as your other medical records. Information about your disease and progress will be sent by your doctors to the **ATLAS** Study Office at the University of Oxford, on paper and electronically, where it will be securely stored under the provisions of the 1998 Data Protection Act and other applicable laws and regulations. All data will be kept in a password protected, encrypted database, and will only be accessible to the research team. We would check with your GP and other professionals involved in your care that there are no medical or other reasons that might make it inappropriate for you to take part in **ATLAS** and also let your GP know that you are taking part in the study. Your details will also be sent to the NHS Information Centre so that NHS and government records can be used to follow your progress. Apart from this, nothing that could reveal your identity will be disclosed outside the research team without your consent. You have the right to check the accuracy of data held about you and to correct any errors. To comply with clinical trial regulations, trial documents will be stored securely after the end of the trial for about 10-15 years and then destroyed.

8. What if there is a problem?

We do not expect that taking part in this research project will cause any problems, but if anyone has a complaint or suffers from any unforeseen harm, they should first speak with the Contact Person named at the foot of this information sheet. If the concerns can not be resolved satisfactorily, study participants can complain formally through the National Health Service complaints mechanisms. Details can, again, be obtained from the Contact Person below. In the event that something does go wrong and you are harmed during your involvement in this research project and this is due to someone's negligence, then you may have grounds for a legal action for compensation against the NHS Trust but you may have to pay your legal costs. Taking part in the **ATLAS** study will not affect your legal rights.

9. What will happen to the findings from the ATLAS study?

Findings will be published in medical journals and will be used by doctors and by other organisations, such as the NHS, to make treatment recommendations. Nothing that could identify you will be included in any report or publication. If you want, we would be pleased to provide study results to you directly on publication of the study.

10. Who is organising and funding the ATLAS study?

The **ATLAS** study was developed and is being organised by a research group from the Universities of London and Oxford. It is funded by the National Institute of Health Research's Health Technology Assessment programme and is sponsored by King's College London. No drug companies are involved in the study.

11. Who has reviewed the research study?

The funding from the HTA to run this study was only granted after a rigorous and extensive review of the research proposal and the way that it would be run. This involved independent experts making a judgement as to the important clinical need as well as the overall design. In addition, the **ATLAS** research study has been reviewed by the London & Surrey Borders Research Ethics Committee who have given approval (reference number 11/LO/1267) for the study to be run in the NHS.

12. What happens next?

If you choose to take part in this research study you will be asked to sign a consent form to confirm this. If you want to think about it for longer, or discuss it with friends or relatives, then you can delay your decision. We will contact you in a few days to answer any questions you might have and, if you wish to participate, enrol you in the study.

Thank you for considering taking part in this research study and taking time to read this information sheet.

Contact Details:

If you would like any further information about this study, then please contact:

Local Trust to enter local contact name, address, email and phone number here

Name: _____

Tel No: _____ **e-mail:** _____

Position: _____

The ATLAS Study Office is located at the Clinical Trial Service Unit, Richard Doll Building, Old Road Campus, Roosevelt Drive, Oxford OX3 7LF.
e-mail: ATLAS2@ctsu.ox.ac.uk; Web address: www.ctsu.ox.ac.uk

APPENDIX B – Patient Consent form

ATLAS - Antipsychotic Treatment of LAte-onset Schizophrenia-like psychosis.

ATLAS Study Number

Initial box to confirm consent

1. I have read and understood the information sheet for the **ATLAS** study (version 1.0, dated 17th July 2011) and have had the opportunity to ask questions.
2. I understand that my participation in this study is voluntary and that, if I take part, I may withdraw at any time, without giving reasons, and without the standard of my medical care or legal rights being affected.
3. I understand that a copy of this consent form and information about me and my progress will be sent in confidence to the study coordinators at the University of Oxford, by my doctors and by NHS registries for use in the **ATLAS** study.
4. I understand that my GP will be informed of my participation in the study and may be contacted to provide information about my progress, in confidence, to the central organisers.
5. I agree that my hospital and other health records may be looked at in confidence by authorised individuals from the **ATLAS** study and by regulatory authorities to check the study is being carried out correctly.
6. I agree that the study researchers may contact me by letter, telephone or email to let me know about progress and results of the **ATLAS** study and to remind me to complete the Quality of Life questionnaires or to ask me the questions over the telephone (if yes, please provide contact details below).

   Yes **No**
7. I understand that all information collected will be held securely, in strict confidence, and used for medical research only and that I will not be identified in any way in the analysis and reporting of the results.
8. I agree to take part in the **ATLAS** study.

Name of Participant _____

Contact details (optional) - Address _____

Telephone: _____ e-mail _____

Signature _____ Date _____

Name of Clinician _____

Signature _____ Date _____

Original to be kept in the **ATLAS** study file, one copy for patient, one kept with patient's notes and one sent to:

ATLAS Study Office, Clinical Trial Service Unit, FREEPOST XXXX,
Richard Doll Building, Old Road Campus, Roosevelt Drive, Oxford OX3 7LF

V1.1 10/12/11

APPENDIX C – BRIEF PSYCHIATRIC RATING SCALE

The BPRS should be administered by a consultant old age psychiatrist or a higher trainee who is knowledgeable concerning psychotic disorders in older people, and able to interpret the constructs used in the assessment

ATLAS Study Number ☐☐☐☐ ☐☐

Date: .....

Patient Name _____

Please enter the score for the term that best describes the patient's condition: 0 = Not assessed, 1 = Not present, 2 = Very mild, 3 = Mild, 4 = Moderate, 5 = Moderately severe, 6 = Severe, 7 = Extremely severe

Score (0 to 7)

1. **SOMATIC CONCERN -** Preoccupation with physical health, fear of physical illness, hypochondriasis. ____
2. **ANXIETY -** Worry, fear, over-concern for present or future, uneasiness. ____
3. **EMOTIONAL WITHDRAWAL -** Lack of spontaneous interaction, isolation deficiency in relating to others. ____
4. **CONCEPTUAL DISORGANIZATION** - Thought processes confused, disconnected, disorganized, disrupted. ____
5. **GUILT FEELINGS** - Self-blame, shame, remorse for past behaviour. ____
6. **TENSION** - Physical and motor manifestations of nervousness, over-activation. ____
7. **MANNERISMS AND POSTURING** - Peculiar, bizarre, unnatural motor behaviour (not including tic). ____
8. **GRANDIOSITY** - Exaggerated self-opinion, arrogance, conviction of unusual power or abilities. ____
9. **DEPRESSIVE MOOD** - Sorrow, sadness, despondency, pessimism. ____
10. **HOSTILITY** - Animosity, contempt, belligerence, disdain for others. ____
11. **SUSPICIOUSNESS** - Mistrust, belief others harbour malicious or discriminatory intent. ____
12. **HALLUCINATORY BEHAVIOR** - Perceptions without normal external stimulus correspondence. ____
13. **MOTOR RETARDATION** - Slowed, weakened movements or speech, reduced body tone. ____
14. **UNCOOPERATIVENESS** - Resistance, guardedness, rejection of authority. ____
15. **UNUSUAL THOUGHT CONTENT** - Unusual, odd, strange, bizarre thought content. ____
16. **BLUNTED AFFECT** - Reduced emotional tone, reduction in formal intensity of feelings, flatness. ____
17. **EXCITEMENT** - Heightened emotional tone, agitation, increased reactivity. ____
18. **DISORIENTATION -** Confusion or lack of proper association for person, place or time ____

Investigator: _____ **TOTAL SCORE** _____

Original to be kept in the **ATLAS** study file, and one copy sent to the **ATLAS** Study Office, Clinical Trial Service Unit, FREEPOST XXXX, Richard Doll Building, Old Road Campus, Roosevelt Drive, Oxford OX3 7LF

APPENDIX D – Simpson – Angus Scale

Patient Name _____

ATLAS Study Number

Date: .....

Please circle the rating for each item:

1. ***Gait*** – The patient's gait, the swing of their arms and their general posture as they walk into the examining room are rated as follows:

0 Normal
1 Diminution in swing while patient is walking
2 Marked diminution in swing with obvious rigidity in the arm
3 Stiff gait with arms held rigidly before abdomen
4 Stooped shuffling gait with propulsion and retropulsion

2. ***Arm Dropping*** - The patient and the examiner both raise to shoulder height and let them fall to their sides. In a normal subject a stout slap is heard as the arms hit the sides. In the patient with severe Parkinson's syndrome the arms fall very slowly:

0 Normal, free fall with loud slap and rebound
1 Fall slowed slightly with less audible contact and little rebound
2 Fall slowed no rebound
3 Marked slowing with no slap at all
4 Arms fall as if against resistance; as though through glue

3***. Shoulder Shaking*** – The subject's arms are bent at a right angle at the elbow and are taken one at a time by the examiner who grasps one hand and also clasps the other around the patient's elbow. The subject's upper arm is pushed to and fro and the humerus is externally rotated. The degree of resistance from normal to extreme rigidity is scored as:

0 Normal
1 Slight stiffness and resistance
2 Moderate stiffness and resistance
3 Marked rigidity with difficulty in passive movement
4 Extreme stiffness and rigidity with almost a frozen shoulder

4***. Elbow Rigidity*** – The elbow joints are separately bent at right angles and passively extended and flexed, with the subject's biceps observed and simultaneously palpated. The resistance to this procedure is rated. (The presence of cogwheel rigidity is noted separately.)

0 Normal
1 Slight stiffness and resistance
2 Moderate stiffness and resistance
3 Marked rigidity with difficulty in passive movement
4 Extreme stiffness and rigidity with almost a frozen shoulder

5. ***Fixation of position or wrist rigidity*** - The wrist is held in one hand and the fingers held by the examiner's other hand, with the wrist moved to extension flexion and both ulnar and radial deviation. The resistance to this procedure is rated as in items 3 and 4.

0 Normal
1 Slight stiffness and resistance
2 Moderate stiffness and resistance
3 Marked rigidity with difficulty in passive movement
4 Extreme stiffness and rigidity with almost a frozen shoulder

6. ***Leg Pendulousness*** - The patient sits on a table with his legs hanging down and swinging free. The ankle is grasped by the examiner and raised until the knee is partially extended. It is then allowed to fall. The resistance to falling and the lack of swinging are scored as:

0 The legs swing freely
1 Slight diminution in the swing of the legs
2 Moderate resistance to swing
3 Marked resistance and damping of swing
4 Complete absence of swing

7. ***Glabella Tap*** – Subject is told to open his eyes wide and not to blink. The glabella region is tapped at a steady, rapid speed. The number of times the patient blinks in succession is noted:

0 0 – 5 blinks
1 6 – 10 blinks
2 11-15 blinks
3 16 –20 blinks
4 21 and more blinks

8. ***Tremor*** – Patient is observed walking into examining room and then is examined for this item:

0 Normal
1 Mild finger tremor, obvious to sight and touch
2 Tremor of hand or arm occurring spasmodically
3 Persistent tremor of one or both limbs
4 Whole body tremor

9. ***Salivation*** – Patient is observed while talking and then asked to open their mouth and elevate their tongue. The following ratings are given:

0 Normal
1 Excess salivation to the extent that pooling takes place if the mouth is open and the tongue raised
2 Excess salivation is present and might occasionally result in difficulty in speaking
3 Speaking with difficulty because of excess salivation
4 Frank drooling

Total Score: _____

Investigator: _____ **Date**: _____

Original to be kept in the **ATLAS** study file, and one copy sent to the **ATLAS** Study Office, Clinical Trial Service Unit, FREEPOST XXXX, Richard Doll Building, Old Road Campus, Roosevelt Drive, Oxford OX3 7LF

APPENDIX E – WHOQOL-BREF

ATLAS Study Number

Date: .....

The following questions ask how you feel about your quality of life, health, or other areas of your life. **Please choose the answer that appears most appropriate.** If you are unsure about which response to give to a question, the first response you think of is often the best one. Please keep in mind your standards, hopes, pleasures and concerns. We ask that you think about your life **in the last four weeks.**

		Very poor	Poor	Neither poor nor good	Good	Very good
1.	How would you rate your quality of life?	1	2	3	4	5

		Very dissatisfied	Dissatisfied	Neither satisfied nor dissatisfied	Satisfied	Very satisfied
2.	How satisfied are you with your health?	1	2	3	4	5

The following questions ask about **how much** you have experienced certain things in the last four weeks.

		Not at all	A little	A moderate amount	Very much	An extreme amount
3.	To what extent do you feel that physical pain prevents you from doing what you need to do?	5	4	3	2	1
4.	How much do you need any medical treatment to function in your daily life?	5	4	3	2	1
5.	How much do you enjoy life?	1	2	3	4	5
6.	To what extent do you feel your life to be meaningful?	1	2	3	4	5

		Not at all	A little	A moderate amount	Very much	Extremely
7.	How well are you able to concentrate?	1	2	3	4	5
8.	How safe do you feel in your daily life?	1	2	3	4	5
9.	How healthy is your physical environment?	1	2	3	4	5

The following questions ask about how completely you experience or were able to do certain things in the last four weeks.

		Not at all	A little	Moderately	Mostly	Completely
10.	Do you have enough energy for everyday life?	1	2	3	4	5
11.	Are you able to accept your bodily appearance?	1	2	3	4	5
12.	Have you enough money to meet your needs?	1	2	3	4	5
13.	How available to you is the information that you need in your day-to-day life?	1	2	3	4	5
14.	To what extent do you have the opportunity for leisure activities?	1	2	3	4	5

		Very poor	Poor	Neither poor nor good	Good	Very good
15.	How well are you able to get around?	1	2	3	4	5

		Very dissatisfied	Dissatisfied	Neither Satisfied nor dissatisfied	Satisfied	Very satisfied
16.	How satisfied are you with your sleep?	1	2	3	4	5
17.	How satisfied are you with your ability to perform your daily living activities?	1	2	3	4	5
18.	How satisfied are you with your capacity for work?	1	2	3	4	5
19.	How satisfied are you with yourself?	1	2	3	4	5
20.	How satisfied are you with your personal relationships?	1	2	3	4	5
21.	How satisfied are you with your sex life?	1	2	3	4	5
22.	How satisfied are you with the support you get from your friends?	1	2	3	4	5
23.	How satisfied are you with the conditions of your living place?	1	2	3	4	5
24.	How satisfied are you with your access to health services?	1	2	3	4	5
25.	How satisfied are you with your transport?	1	2	3	4	5

The following question refers to how often you have felt or experienced certain things in the last four weeks.

		Never	Seldom	Quite often	Very often	Always
26.	How often do you have negative feelings such as blue mood, despair, anxiety, depression?	5	4	3	2	1

Do you have any comments about the assessment?

[The following table should be completed after the interview is finished]

		Equations for computing domain scores	Raw score	Transformed scores*	
				4-20	0-100
27.	**Domain 1**	(6-Q3) + (6-Q4) + Q10 + Q15 + Q16 + Q17 + Q18 ++++++	a. =	b:	c:
28.	**Domain 2**	Q5 + Q6 + Q7 + Q11 + Q19 + (6-Q26) + + +++	a. =	b:	c:
29.	**Domain 3**	Q20 + Q21 + Q22 ++	a. =	b:	c:
30.	**Domain 4**	Q8 + Q9 + Q12 + Q13 + Q14 + Q23 + Q24 + Q25 + + +++++	a. =	b:	c:

* See Procedures Manual, pages 13-15

APPENDIX F – CLIENT SERVICE RECEIPT INVENTORY

ATLAS Study Number

Date: .....

A. PATIENT'S ACCOMMODATION

1. What has been the patient's usual place of residence during the last 6 months? ***Circle one box***

1	**Owner occupied house/flat**	**Go to Q2**
2	**Privately rented house/flat**	**Go to Q2**
3	**House/flat rented from housing association/local authority**	**Go to Q2**
4	**Care home (residential/care only)**	**Go to Q3**
5	**Nursing home**	**Go to Q3**
6	**Other (specify)**	**Go to Q1a**
55	*Not applicable*	
77	*Does not know answer*	
88	*Unwilling to answer question (though able)*	

1a	**Other (specify)**	

2. Is accommodation "sheltered" (has a warden or scheme manager on-site)?

1	**Yes**	**Go to Q4**
0	**No**	**Go to Q4**
77	*Does not know answer*	

3. Please give the name of the organisation managing the facility and *tick* whether this is local authority adult social services, an NHS organisation, private (for-profit) organisation, voluntary (non-profit) organisation or other.

1	**Local authority social services**	**Go to Q4**
2	**NHS**	**Go to Q4**
3	**Private (for-profit)**	**Go to Q4**
4	**Voluntary (non-profit)**	**Go to Q4**
5	**Other**	**Go to Q3a**
55	*Not applicable*	
77	*Does not know answer*	
88	*Unwilling to answer question (though able)*	

3a	**Other (specify)**	

4.. What is the patient's total contribution to weekly charge for facility?	
£ ☐☐☐☐.☐☐	
55	*Not applicable*
77	*Does not know answer*
88	*Unwilling to answer question (though able)*

5. Who contributes to the cost of this placement? ***Circle all that apply***

1	**NHS**	**Go to Q6**
2	**Local authority**	**Go to Q6**
3	**Voluntary organisation/charity**	**Go to Q6**
4	**Social security benefits**	**Go to Q6**
5	**Patient** *(savings, pension, other income from investments)*	**Go to Q6**
6	**Patient's family**	**Go to Q6**
7	**Insurance policy**	**Go to Q6**
8	**Other (specify)**	**Go to Q5a**
77	*Does not know answer*	
88	*Unwilling to answer question (though able)*	

5a	**Other (specify)**	

6. Apart from holidays or visits to family and friends, has the patient lived anywhere else during the last 6 months? *Please exclude hospital* admissions as these will be recorded below.

1	**Yes**	**Go to Q7**
0	**No**	**Go to Q8**
77	*Does not know answer*	

7. **If yes** to Question 6, what type of accommodation was this and approximately how many nights were spent there in the last 6 months?

Accommodation type		**Approximate number of nights in last 6 months**	
1	**Care home (residential/care only)**		**Go to Q8**
2	**Nursing home**		**Go to Q8**
3	**Other** ***(please specify)***		**Go to Q8a**
77	*Does not know answer*		
88	*Unwilling to answer question (though able)*		

7a	**Other (specify)**	

B. SERVICES USED

8. Has the patient used any **hospital services** over the last 6 months?

1	**Yes**	**Go to Q9**
0	**No**	**Go to Q10**
77	*Does not know answer*	
88	*Unwilling to answer question (though able)*	

9. **If yes**, please provide details of **hospital services** you have used in the last 6 months below:

		Accident and emergency	**Code 01**
		Day hospital	**Code 02**
		Inpatient care	**Code 03**
		Outpatient care	**Code 04**
Code	**Reason for attendance / stay** (please enter different details of reasons/events on separate lines)	**Reason for admission**	**Number of attendances / overnight stays in last 6 months**

10. Has the patient used any **community-based** services *as a result of their mental health problems* over the last 6 months?

1	**Yes**	**Go to Q11**
0	**No**	**Go to Q12**
77	*Does not know answer*	
88	*Unwilling to answer question (though able)*	

11. **If yes**, please indicate any use the patient has made of **community-based services** over the last 6 months. *Please do not include any services already recorded at Q9.* :

Primary Care, Community Health or Emergency Services		Used?	No. of contacts	Typical duration
1.	Community/District nurse	**YES NO**		
2.	Practice nurse	**YES NO**		
3.	Night nurse	**YES NO**		
4.	Occupational therapist	**YES NO**		
5.	Physiotherapist	**YES NO**		
6.	General practitioner	**YES NO**		
7.	Other community doctor	**YES NO**		

Social care service		Used?	No. of contacts	Typical duration
8.	Social worker or Care manager	**YES NO**		
9.	Home care/home help worker	**YES NO**		
10.	Private home help/cleaner	**YES NO**		
11.	Night sitter/paid carer	**YES NO**		
12.	Has the patient pressed personal alarm button for help?	**YES NO**		

Community Mental Health Services		Used?	No. of contacts	Typical duration
13.	Psychologist	**YES NO**		
14.	Psychiatrist	**YES NO**		
15.	Community psychiatric nurse / Community mental health nurse	**YES NO**		

11a	Other mental health professional (*please specify)*			
11b	Other mental health professional (*please specify)*			

Other Health Services not mentioned above e.g. optician, dentist		Used?	No. of contacts	Typical duration
11c	Other health service not mentioned above (*please specify)*			
11d	Other mental health professional (*please specify)*			

12. Has the patient used any medications over the last 6 months?		
1	**Yes**	**Go to Q13**
0	**No**	**Go to Q14**
77	*Patient does not know answer*	
88	*Unwilling to answer question (though able)*	

13. **If yes**, please indicate any medications used over the last 6 months:

Name of medication	Dosage if known (mg)	Dose frequency (e.g. daily)	For how long has the patient taken this drug?
1.			
2.			
3.			
4.			
5.			
6.			

Go to Q14

C. SUPPORT PROVIDED BY (UNPAID) CARERS

14. Does the patient have an informal carer (unpaid)?		
1	**Yes**	**Go to Q15**
0	**No**	**END OF FORM**
88	*Unwilling to answer question (though able)*	

(Note: If the patient is supported by several informal carers, please answer Q15 and subsequent questions about the main carer.)

15. **If yes**, does this **principal** carer live in the same household

1	**Carer lives in**	**Go to Q16**
0	**Carer does not live in**	**Go to Q16**
88	*Unwilling to answer question (though able)*	

16. What is the **principal** carer's **main** employment status? ***(Tick one box)***

0	**Employed full time** *(working 30 hours or more per week)*	**Go to Q17**
1	**Employed part-time** *(working less than 30 hours per week)*	**Go to Q17**
2	**Self-employed**	**Go to Q17**
3	**Unemployed**	**END OF FORM**
4	**Volunteer**	**Go to Q17**
5	**Retired** *(due to age)*	**END OF FORM**
6	**Retired** *(due to ill health)*	**END OF FORM**
7	**Student**	**END OF FORM**
8	**Housewife/Househusband**	**END OF FORM**
9	**Other (specify)**	**Go to Q16a**
77	*Does not know answer*	
88	*Unwilling to answer question (though able)*	

16a	**Other (specify)**	

17. If **employed or a volunteer**, please describe the current job or voluntary activity

a) Occupation _____

b) Job title _____

Go to Q18

18. How many hours does the carer typically work each week <u>over the last 6 months</u> in all employment or volunteering activities?		
Hours per week		**Go to Q19**
88	*Unwilling to answer question (though able)*	

19. Has the carer taken days off work or volunteering <u>over the last 6 months</u> in order to provide care for this patient?		
1	**Yes**	**Go to Q20**
0	**No**	**Go to Q21**
88	*Unwilling to answer question (though able)*	

20. If yes, how many days in the <u>last 6 months</u>?.....days		
88	*Unwilling to answer question (though able)*	**Go to Q21**

21. Have there been any days in the <u>last 6 months</u> when the patient's behaviour / needs meant that the carer could not work (or act as a volunteer) as well as they would usually do?		
1	**Yes**	**Go to Q22**
0	**No**	**END OF FORM**
88	*Unwilling to answer question (though able)*	

22. If yes, how many days in the <u>last 6 months</u>? .....days		
88	*Unwilling to answer question (though able)*	**END OF FORM**

Original to be kept in the **ATLAS** study file, and one copy sent to the **ATLAS** Study Office, Clinical Trial Service Unit, FREEPOST XXXX, Richard Doll Building, Old Road Campus, Roosevelt Drive, Oxford OX3 7LF

ATLAS Study Number ☐☐☐☐ ☐☐

Date: .....

EuroQol Questionnaire (EQ-5D)

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑

I have some problems in walking about ❑

I am confined to bed ❑

Self-Care

I have no problems with self-care ❑

I have some problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑

I have some problems with performing my usual activities ❑

I am unable to perform my usual activities ❑

Pain/Discomfort

I have no pain or discomfort ❑

I have moderate pain or discomfort ❑

I have extreme pain or discomfort ❑

Anxiety/Depression

I am not anxious or depressed ❑

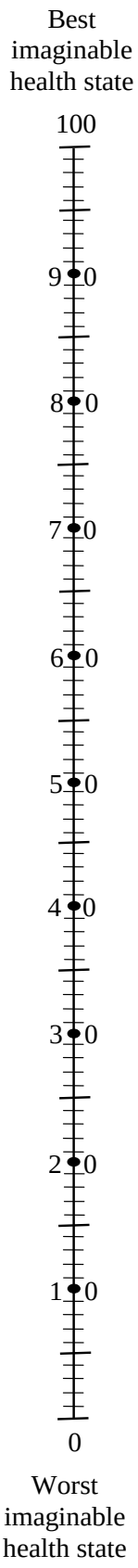
I am moderately anxious or depressed ❑

I am extremely anxious or depressed ❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



APPENDIX H – Randomisation Notepad

ATLAS - Registration and Randomisation form

Once a potentially eligible patient is identified, the **ATLAS** Study Office should be informed (by telephone, fax or e-mail) and the information in parts A and B below provided. If not already supplied, an **ATLAS** patient treatment pack will be sent to the hospital pharmacy within two working days so that treatment can be given to the patient if they consent to be randomised at the second appointment to discuss the trial information and seek the patient's consent to participate (see Protocol section 4.3 Randomisation). N.B. If the patient does not agree to randomisation, the ATLAS Study Office should be notified so they know that the treatment pack has not been obtained from the hospital pharmacy. Reasons why eligible patients are not invited, or do not consent, to take part should be recorded on the screening log in the ATLAS study folder.

The details below will be requested for each potential participant. It may be helpful to prepare for these questions by filling in this pad before telephoning the **ATLAS** Study Office's toll free randomisation service on 0800 585323.

PART A: REGISTRATION: HOSPITAL AND PATIENT DETAILS

Responsible Consultant .....**Hospital** .....

Patient's initials .... **Age (must be ≥60)** ..... **Sex:** **M** ☐ **F** ☐

Living with spouse/partner ☐ **Living alone** ☐ **Other** ☐ **Specify**..... ....

Ethnic group: **White** ☐ **Black** ☐ **Asian** ☐ **Chinese** ☐ **Mixed** ☐ **Other** ☐ **Specify:** .....

PART B: REGISTRATION: ELIGIBILITY CHECKLIST

Late (age≥60) onset schizophrenia like psychosis? **Yes** ☐ **No** ☒ **(ineligible)** **Approx. duration of symptoms:** .....months

Able to give informed consent? **Yes** ☐ **No** ☒ **(ineligible)** **Dependent on carer? No** ☐ **Yes** ☐

BPRS score: ..... **BPRS < 30?**	**No** ☐	**Yes** ☒	**(if yes, care must assent)**
Primary diagnosis of affective disorder?	**No** ☐	**Yes** ☒	
Significant cognitive impairment and MMSE score <25?	**No** ☐	**Yes** ☒	If 'yes' to <u>any</u> of these questions, the patient is <u>ineligible</u> for randomisation
Uncontrolled serious concomitant illness?	**No** ☐	**Yes** ☒	
Contraindication to amisulpride?	**No** ☐	**Yes** ☒	
Prescribed amisulpride in last 28 days?	**No** ☐	**Yes** ☒	

Amisulpride, or other antipsychotic drug (now or previously)? **No** ☐ **Yes, previously** ☐ **Yes, currently (≤28 days)** ☐

Specify which drug(s): _____

PART C: RANDOMISATION: ADDITIONAL DETAILS & TREATMENT ALLOCATION

Patients' full name .....

If available: **Hospital number:** ..... **NHS. Number:** ..... **GP:**.....

MMSE score ..... **Weight** ..... **Hypertensive treatment?** **Yes** ☐ **No** ☐

ATLAS Study No. ☐☐☐☐ ***(Pack with this number to be collected from pharmacy)***

Contact Person (for any queries) _____ **Telephone** _____

Original to be kept in the **ATLAS** study file and one copy sent to the **ATLAS** Study Office, Clinical Trial Service Unit, FREEPOST XXXX, Richard Doll Building, Old Road Campus, Roosevelt Drive, Oxford OX3 7LF.

APPENDIX I – Specimen letter to GP

To be printed on local Trust headed paper

GP name
Surgery
Street name
City
Postcode

Date

Dear Dr

Name _____ D.o.B _____ NHS No _____

Your patient, named above, has been diagnosed with late (i.e. ≥60 years) onset schizophrenia like psychosis. Treatment with a low dose of an atypical antipsychotic may be helpful and such treatment is widely used. However, there is no reliable randomised clinical trial evidence to support this practice and there are concerns about the safety of antipsychotic treatment in older patients. We are, therefore, taking part in the national **ATLAS** double-blind randomised trial of amisulpride for late onset psychosis, which aims to determine the balance of benefits and risks of amisulpride more reliably. Patients who take part in the trial receive an initial 12-week course of treatment with either amisulpride (100mg/day) or placebo. This is followed by a further 24 weeks of treatment, again with either amisulpride or placebo. Patients receiving placebo in the first 12 weeks switch to amisulpride and so all patients receive active treatment at some stage of the trial.

Your patient has kindly agreed to take part in ATLAS and has been prescribed their first 12 weeks of treatment. We will re-assess the patient in 4 weeks time and then again a week or two before they complete their 12-week course of capsules. If the patient remains compliant with the study treatment a further 24-week course will be dispensed and the patient re-assessed towards the end of this course. We do not expect that amisulpride at this low dosage will cause many side-effects but, if your patient does experience possible side-effects, please contact the ATLAS study office for guidance.

ATLAS was developed and is being jointly coordinated by a research group from the Universities of London and Oxford. The **ATLAS** Study Office is located at the University of Oxford's Clinical Trial Service Unit (address below). The study is funded by the National Institute of Health Research's Health Technology Assessment programme and receives no commercial support. The trial has been approved by London & Surrey Borders Research Ethics Committee and the Local Research Ethics Committee at each participating centre.

I, or another member of the team responsible for your patient, will update you on the patient's progress. If you have any queries about the patient's management, please feel free to contact me. If you require any further information about the **ATLAS** trial, it can be obtained from the **ATLAS** study office (see address below). Please file this letter in the patient's notes. I would appreciate being notified if they are no longer one of your patients.

Yours sincerely

The **ATLAS** Study Office, CTSU, FREEPOST XXXX-XXXX-XXXX, Richard Doll Building, Old Road Campus, Roosevelt Drive, Oxford OX2 7LF. Tel: 01865 415 743537; Fax: 01865 743982; Email: ATLAS@ctsu.ox.ac.uk www.ATLAS.ctsu.ox.ac.uk

V1.0 17/7/11

APPENDIX J – Patient follow-up form

ATLAS PATIENT FOLLOW-UP

ATLAS Study Number ☐☐☐☐ ☐☐

Date: .....

Assessment (circle): 4 weeks / 10-12 weeks / 34-36 weeks

Please provide the following details:

Patient's Name: .....

Address: .....

If the patient has moved recently, please give reason: .....

Has the patient developed any side effects thought to be due to ATLAS treatment?

No ☐ Yes ☐ If YES, what were these side-effects: .....

Were any side effects serious adverse events (i.e. fatal, life-threatening, required hospitalisation or prolongation of existing hospitalisation, or resulted in significant disability or incapacity)?

No ☐ Yes ☐ If yes, has SAE form been completed? Yes ☐ No ☐ (Please complete SAE form)

Has patient taken all scheduled ATLAS capsules? No, stopped ☐ No, missed some ☐ Yes ☐

If **NO**, what was the main reason for stopping/ missing capsules? .....

Date of stopping: ..... Number of capsules returned/missed: .....

Is the patient taking any other drug treatment(s)? No ☐ Yes ☐

If YES, which drug(s), what dose, when started and why? .....

Name of person completing form ..... Today's Date .....

Telephone number ..... e-mail .....

Thank you for your help

Return to: **ATLAS** Study Office, CTSU, FREEPOST XX-XXXX-XXXX, Richard Doll Building, Old Road Campus, Roosevelt Drive, Oxford OX2 7LF. Tel: 01865 415 743537; Fax: 01865 743982; Email: ATLAS@ctsu.ox.ac.uk www.ATLAS.ctsu.ox.ac.uk

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APPENDIX K – Serious Adverse Event Form

Please report immediately any SAEs (see protocol page 11 for definition), or if the patient dies of any cause, by completing all the details below and faxing this form to the ATLAS Study Office on 01865 743982

Patient's name: _____ Date of Birth: ____/____/____

NHS No: _____ Hospital No: _____ **ATLAS** No: |_|_|_|_|

Responsible Psychiatrist: _____ Hospital: _____

SAE description

Is this an initial or follow up report Initial ☐ Follow up ☐ Is this final report? Yes ☐ No ☐

Reason for reporting:

Life threatening event? Yes ☐ Fatal event? Yes ☐ Date of death ___/___/____

Required hospitalisation? Yes ☐ No. of days? _____

Persistent or significant disability/incapacity? Yes ☐ Other reason for reporting? Yes ☐

If other, please specify: _____

Date event started: ____/____/____ Date event ceased: ____/____/____

What was the outcome of the SAE? Fatal ☐ Recovered ☐ Continuing ☐

Details of adverse event (please attach copies of relevant reports): _____

_____

_____

Trial treatment Is SAE related to ATLAS treatment? Yes ☐ No ☐

If SAE considered to be related to treatment, please assess causality (**must be completed by a clinician**):

Causality assessment codes -: (circle most likely code):
1 Probably unrelated to treatment 2 Possibly related to treatment
3 Probably related to treatment 4 Definitely related to treatment

Please give reasons if you consider the event to be possibly, probably or definitely treatment related:

_____

_____

Was the SAE **unexpected**, i.e. of a **type** or **severity** which is NOT consistent with the up-to-date SPC (available at http://emc.medicines.org.uk/)? **This section must be completed by a clinician**

Unexpected ☐ Expected ☐

Please give reasons if you consider the event to be unexpected: _____

_____

_____

Signature of Person Reporting: _____ Date: ____/____/___

You must have signed the Site Delegation Log

Name: _____ Position: _____

Telephone number: _____

Signature of Investigator: _____ Date: ____/____/____

If not completed by Investigator

SUSAR Reporting – CTSU USE ONLY

SAE reference number: _____ Date reported to CTSU: _____/_____/_____

Date reported to CI: _____/_____/_____Date reply received from CI: _____/_____/_____

Is this event a SUSAR? Yes ☐ If Yes: 7 day report ☐ OR 15 day report ☐

No ☐ If No, is this an SAE? Yes ☐ No ☐

CI comments: _____

_____

_____

Date due to be reported to MHRA and MREC: _____/_____/_____

When you have faxed the form, please then send (with copies of any relevant reports) to:
The ATLAS Study Office, CTSU, FREEPOST XXXX-XXXX-XXXX, Richard Doll Building,
Old Road Campus, Roosevelt Drive, Oxford OX2 7LF

V1.0 2/05/11

APPENDIX L – REFERENCES

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